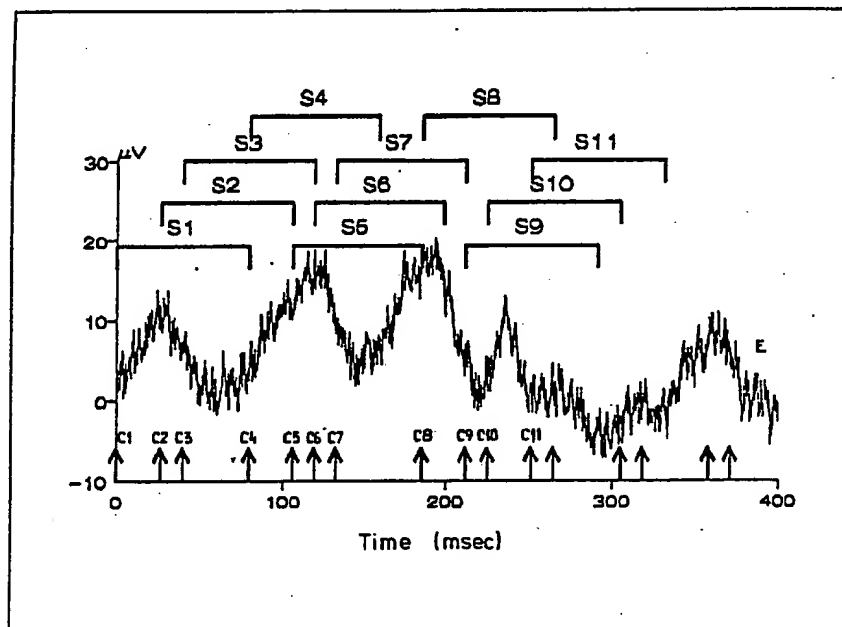




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61B 5/0476	A1	(11) International Publication Number: WO 91/19453 (43) International Publication Date: 26 December 1991 (26.12.91)
(21) International Application Number: PCT/NL91/00096 (22) International Filing Date: 13 June 1991 (13.06.91) (30) Priority data: 9001341 13 June 1990 (13.06.90) NL (71) Applicant (for all designated States except US): STICHTING VOOR DE TECHNISCHE WETENSCHAPPEN [NL/ NL]; Van Vollenhovenlaan 661, NL-3527 JP Utrecht (NL). (72) Inventor; and (75) Inventor/Applicant (for US only): CLUITMANS, Petrus, Jo- hannes, Maria [NL/NL]; Zoete Kroon 17, NL-4191 DV Geldermalsen (NL). (74) Agents: DE BRUIJN, Leendert, C. et al.; Nederlandsch Octrooibureau, Scheveningsweg 82, P.O. Box 29720, NL-2502 LS The Hague (NL).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (Eu- ropean patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European pa- tent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: METHOD FOR DETERMINING ANAESTHETIC DEPTH**(57) Abstract**

Method for determining the anaesthetic depth of a patient, comprising the repeated administering of sensory stimuli to the patient; the repeated, non-invasive recording of the electrical activity of the patient's brain during a measurement interval following each stimulus; the computation, from a number of measurement intervals, of a representation of the response of a sensory neural pathway to a single stimulus; and the determination of the latencies and amplitudes of maxima and minima in the representation, which are a measure of the anaesthetic depth, wherein the measurement intervals are chosen such that they partially overlap one another. Preferably the length of time between two successive stimuli is a stochastic variable having a negative exponential distribution, the computed representation being the first order kernel.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

Method for determining anaesthetic depth

5

The invention relates to a method for determining the anaesthetic depth of a patient, comprising the following steps:

- the repeated administering of sensory stimuli to the patient;
- the repeated, non-invasive recording of the electrical
- 10 activity of the patient's brain during a measurement interval following every stimulus;
- the computation, from a number of measurement intervals, of a representation of the response of a sensory neural pathway to a single stimulus; and
- 15 - the determination of the latencies and amplitudes of maxima and minima in the representation, which are a measure of the anaesthetic depth.

A method of this type is known in practice.

Modern anaesthetic techniques frequently make use of

20 combinations of substances having different effects. By this means the four aspects of anaesthesia, that is to say unconsciousness, suppression of the perception of pain stimuli (analgesia), reduction of autonomic reflexes and suppression of muscular functions (relaxation) can be regulated more or less independently

25 of one another. The original way of determining the anaesthetic depth on the basis of clinical observations and measurements can, however, no longer be used in this case. To still provide a reliable indication of the anaesthetic depth, in order, inter alia, to prevent the patient regaining consciousness during the

30 operation, new techniques for determining the anaesthetic depth are being sought.

A technique of this type is the method mentioned in the preamble. With a method of this type, the electrical response of a sensory neural pathway as a result of a sensory stimulus is

35 measured. This response is distinguished by a characteristic sequence of maxima and minima. Groups of these maxima and minima are classified in components on the basis of their neurological generators. The brain stem components are, for example, generated

in the brain stem and the middle latency components in the midbrain and the primary cerebral cortex. As the anaesthetic depth increases, the latency of the components, that is to say the time period between the administering of the sensory stimulus and the occurrence of a specific minimum or maximum in the electrical response, increases, while in general the amplitude of the minimum or maximum decreases. Consequently, the latency and the amplitude of the response can be used as a measure of the anaesthetic depth.

However, with this procedure the problem arises that the amplitude of the response is very many times smaller than the amplitude of the spontaneous activity generated by the brain. Since, with respect to the measurement of the response, this spontaneous activity can be regarded as noise, the desired signal has a very poor signal-to-noise ratio relative to the measured signal, the electroencephalogram (EEG). In the case of the known method, the signal-to-noise ratio is improved by averaging a large number, for example 1,000, measured responses. In principle the noise is averaged out because of this, so that an "average response" results which is representative for the response to a single stimulus and which has a good signal-to-noise ratio. The latency and the amplitude of specific components in the response can now be determined with sufficient accuracy from this "average response".

In order to obtain a reliable result, the measurement intervals according to the known method are chosen such that no or only minimal interference occurs between the successive responses, that is to say a stimulus is administered only when the response to the preceding stimulus has virtually completely vanished. With this procedure, however, the problem arises that the total measurement time required is long. In the case of administering, for example, ten stimuli per second, a measurement time of one hundred seconds, that is to say almost two minutes, is needed for averaging one thousand measurement intervals. This measurement time is too long for most applications.

The aim of the invention is to overcome this disadvantage and to provide a method with which the anaesthetic depth can be determined accurately in an appreciably shorter period. To this end, the method according to the invention is characterised in that

the measurement intervals are chosen such that they partially overlap one another.

As a result of the partial overlapping of the measurement intervals, the average frequency with which the stimuli are administered can be much higher, for example one hundred stimuli per second. For the number of one thousand measurement intervals, the total measurement time is consequently only ten seconds.

In the case of overlapping measurement intervals, interference can arise between two or more successive responses. The adverse effect of interfering responses on the measurement results can be reduced by randomly varying the length of time between two successive stimuli, that is to say by choosing a stochastic variable for said length of time. However, the interference can then still result in an inadmissible distortion of the signal shape determined from the measurement intervals. According to the invention, the interference between successive responses in the case of overlapping measurement intervals is averaged out if the (stochastic) length of time between two successive stimuli is chosen such that said length of time has a negative exponential distribution.

A further problem which can arise in the case of overlapping measurement intervals is the fact that the neural pathway for which the response is measured starts to behave as a non-linear system. In the case of the averaging of the signals recorded in the measurement intervals, which is known from the prior art, it is assumed that the neural pathway constitutes a linear system. This signifies that because of the non-linearities the averaging process known from the prior art can yield an inaccurate result. According to the invention this problem is avoided by computing the representative response on the basis of a non-linear model of the neural pathway. To this end the method according to the invention is characterised in that the computed representation is the first order kernel.

Various senses can be stimulated to generate the responses to be measured. In the case of the method according to the invention, it is preferably the hearing which is stimulated, since this can be carried out simply without adverse consequences for the patient.

The method according to the invention will be illustrated in

more detail below with reference to a preferred embodiment, for which by way of illustration:

Figure 1 shows an electroencephalogram with the sensory stimuli administered and the associated measurement intervals, and

5 Figure 2 shows a few shapes of a computed representation for various levels of anaesthetic depth.

Earphones which produce clicking noises are used for administering sensory stimuli. The times at which the clicks occur are chosen randomly, specifically in such a way that the length of time between two successive clicks is a stochastic variable with a negative exponential distribution. Consequently, the number of clicks occurring within a fixed time interval is a stochastic variable having a Poisson distribution. A series of time intervals having a negative exponential distribution can be obtained by means of an algorithm such as is described in "The Art of Computer Programming", part 2, by D.E. Knuth (Addison Wesley, 1969). On average, approximately one hundred clicks are supplied per second. Each click is followed by a measurement interval approximately 80 msec long. This is shown schematically in Figure 1, in which the time in milliseconds is shown on the horizontal axis and the signal amplitudes in microvolts on the vertical axis. Here the start times of each of the measurement intervals S1-S11 shown coincide with the times at which the clicks C1-C11 occur. E is the continuously recorded electroencephalogram, a section of which is each time processed separately, in each of the overlapping intervals S1-S11.

The electroencephalogram is recorded with the aid of electrodes, of which one is applied to one of the patient's ears, one on the top of the skull and one as a reference electrode on the forehead. The recorded signal is digitalised and stored electronically. The first order kernel is then determined by means of the expression:

$$h_1(T) = \frac{1}{\sigma} \sum_{n=0}^{N-1} y_1(t) \cdot \{x(t-T)-\sigma\}$$

where:

$h_1(T)$ is the first order kernel at time T

σ is the average stimulus frequency

N is the number of measurement intervals
 $y_i(t)$ is the measured signal in measurement interval i
 $x(t)$ is the signal supplied to the earphones.

Figure 2, in which, once again, the time in ms is plotted on the horizontal axis and the signal amplitudes in μV on the vertical axis, shows a few first order kernels computed in this way for various levels of anaesthetic depth. In particular in the case of the low-frequency component, it can clearly be seen how both the amplitudes and the times of occurrence of specific maxima and minima change as the anaesthetic depth changes.

The computation of the first order kernel can be carried out during the recording of the electroencephalogram, that is to say the values of $y_i(t)$ for a specific measurement interval are processed in the computation as soon as they are available. A further gain in speed is achieved in this way, since the first order kernel will now be available virtually immediately after the final measurement interval. The storage of the measurement data and the execution of the computation of the first order kernel can be carried out by means of time sharing on a single processor, if necessary assisted by a mathematical co-processor. Of course, two independent processors can also be used.

The latency and amplitude of the first order kernel, which for linear systems is identical to the pulse response, are determined at the times at which minimum and maximum amplitudes occur. The latencies and amplitudes can be compared with latencies and amplitudes measured before the narcosis, the increase in the latency and the decrease in the amplitude being a measure for the anaesthetic depth. The amplitude of the first order kernel decreases to a lesser extent as the anaesthetic depth increases than does the amplitude of the pulse response employed in the prior art. Consequently, the first order kernel has a better signal-to-noise ratio for a greater anaesthetic depth than does the pulse response.

An apparatus for carrying out the method according to the invention comprises a pulse generator for generating pulses, which are administered to the patient as sensory stimuli by means of a transducer. Thus, for example, short-duration pulses can be supplied to earphones, which pulses are converted to clicks by the

earphones. In this case the pulse generator is preferably designed such that the number of pulses occurring within a specific time interval is preferably a stochastic variable having a Poisson distribution. A pulse generator of this type can be a programmable
5 pulse generator or a pulse generator with a fixed algorithm for generating pulses with the desired distribution.

An apparatus of this type also comprises amplifiers for amplifying the EEG signals, recorded with the aid of electrodes, and analogue-to-digital converters for digitalising said signals.
10 Furthermore, storage means, such as a RAM memory or a magnetic disc, are provided for storing the digitalised signal and a processing unit is also provided. The processing unit, which can be a general purpose computer, computes a representation of the response of a sensory neural pathway to a single stimulus from the signal
15 values within a large number of measurement intervals synchronised with the stimuli. With this procedure the measurement intervals will partially overlap one another, so that the processing unit will use some signal values in the computation several times. Preferably, the processing unit is programmed such that the
20 computed representation is the first order kernel. The apparatus for carrying out the method according to the invention also comprises output means, such as a screen, for displaying the computed representation. The apparatus can optionally comprise means for the direct computation of the latency and the amplitude
25 from the representation, output means then being present for displaying the computed values.

CLAIMS

1. Method for determining the anaesthetic depth of a patient, comprising the following steps:
 - 5 - the repeated administering of sensory stimuli to the patient;
 - the repeated, non-invasive recording of the electrical activity of the patient's brain during a measurement interval following each stimulus;
 - the computation, from a number of measurement intervals, of a representation of the response of a sensory neural pathway to a single stimulus; and
 - 10 - the determination of the latencies and amplitudes of maxima and minima in the representation, which are a measure of the anaesthetic depth,
 - 15 characterised in that the measurement intervals are chosen such that they partially overlap one another.
2. Method according to Claim 1, in which the length of time between two successive stimuli is a stochastic variable, characterised in that this stochastic variable has a negative exponential distribution.
- 20 3. Method according to Claim 1 or 2, characterised in that the computed representation is the first order kernel.
4. Method according to one of the preceding claims, characterised in that the sensory stimuli are auditory stimuli.
- 25 5. Apparatus for carrying out a method according to one of the preceding claims, comprising:
 - means for generating sensory stimuli having a random time distribution;
 - means for the non-invasive recording, during a number of measurement intervals, of the electrical activity of the patient's brain;
 - 30 - means for converting the recorded electrical activity into digital values;
 - means for computing the representation of the response of a sensory neural pathway to a single stimulus; and
 - 35 - means for displaying the representation,characterised in that the said means for generating the sensory stimuli are arranged such that the length of time between two

successive stimuli has a negative exponential distribution, and in that the said means for recording arrange the measurement intervals such that said intervals partially overlap one another.

6. Apparatus according to Claim 5, characterised in that the
- 5 said means for computing the representation arranged for the computation of the first order kernel.

fig-1

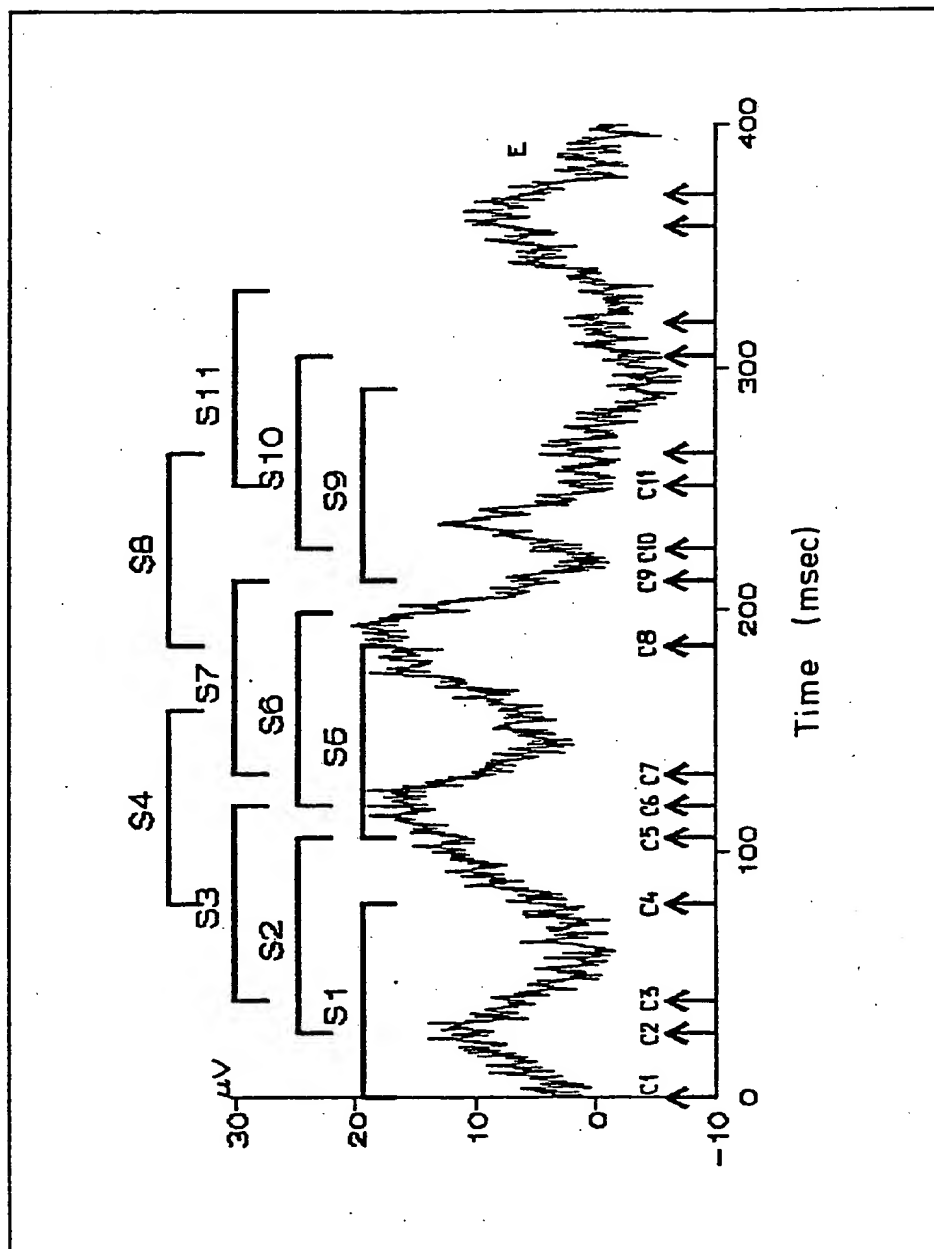
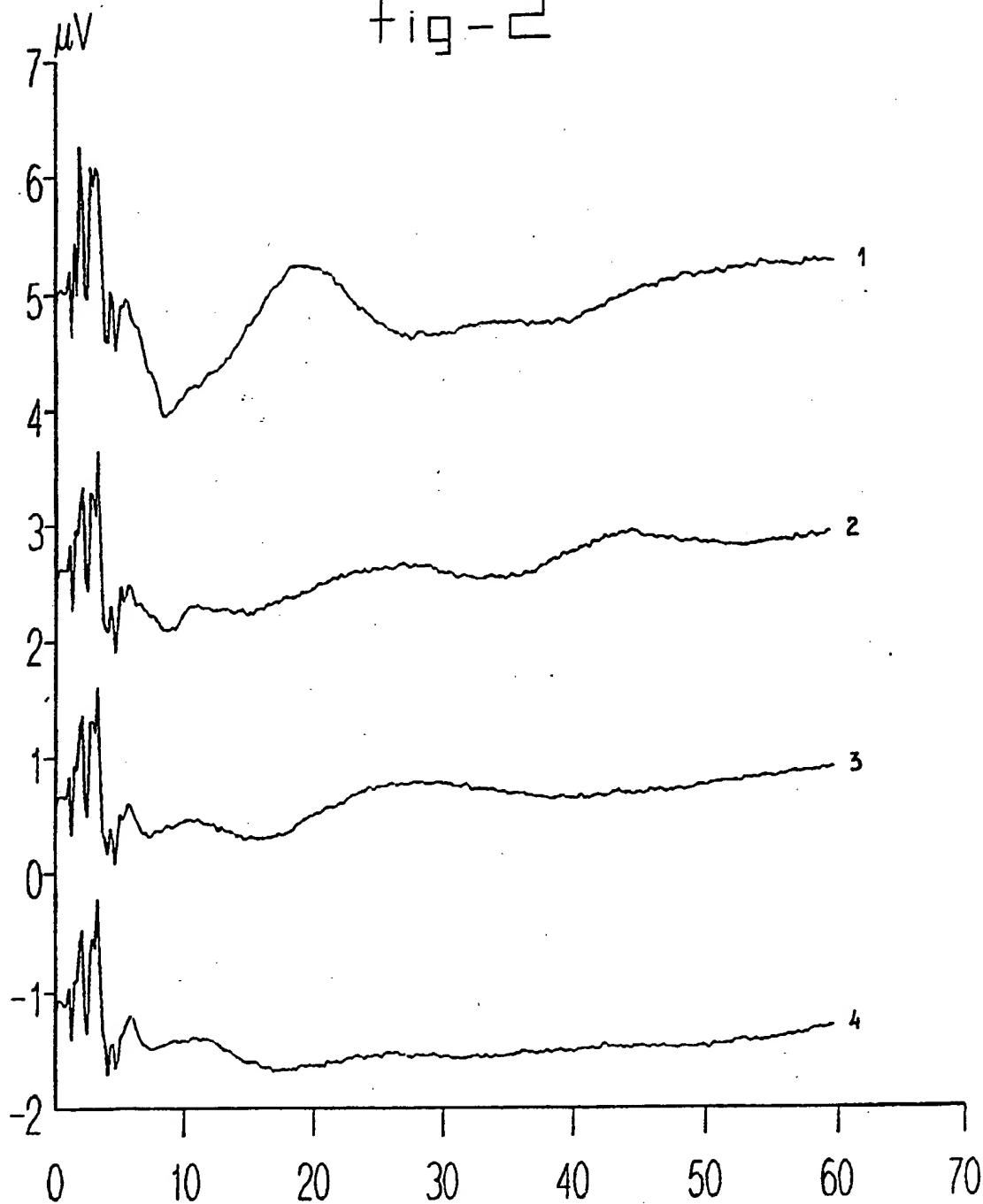


fig-2



INTERNATIONAL SEARCH REPORT

PCT/NL 91/00096

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61B5/0476		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61B ; A61M	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US,A,4201224 (JOHN) 06 May 1980 see figure 2 see column 5, line 20 - column 12, line 68 ---	1, 2, 4, 5
A	TRANSACTIONS OF THE INSTITUTE OF ELECTRONICS AND COMMUNICATION ENGINEERS OF JAPAN, SECTION E. vol. E66, no. 4, April 1983, TOKYO JP. pages 252 - 253; MAGATANI et al.: "Evoked responses in general anesthesia." see the whole document ---	1, 4, 5
A	US,A,3513834 (SUZUKI ET AL.) 26 May 1970 see figures 1-5 see column 3, line 49 - column 8, line 24 ---	1, 5
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10 SEPTEMBER 1991	11. 10. 91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	CHEN A.H. <i>A. Chen</i>	

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

NL 91/00096

SA 48852

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

10/09/91

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4201224	06-05-80	CA-A- 1144605	12-04-83
		EP-A,B 0013183	09-07-80
		JP-A- 55091337	10-07-80

US-A-3513834	26-05-70	None	
